Remarks

Introduction

Prior to entry of the claim amendments presented above, claims 21-35 were pending in the application. The amendments are fully supported by the specification. Claims 36-40 are added and present no new matter. Claims 21-40 are thus pending for reexamination and reconsideration, which are respectfully requested in view of the foregoing amendments and following remarks.

In the May 28, 2002 Office Action, claims 21-35 were rejected under 35 USC §112, first paragraph, as non-enabled, and second paragraph, as indefinite. The specific grounds for rejection, and applicants response thereto, are set out in detail below.

Claim Objections

Claims 21-35 are objected to because liposome is misspelled. Applicants have amended the claims to correct this obvious typographical error.

Claim Rejections Under 35 U.S.C. § 112, first paragraph

The Examiner alleges that claims 21-35 are not enabled by the specification. Specifically, the Examiner asserts that 1) RNA results in poorer gene expression than does DNA delivery, and 2) there are major problems with gene therapy in general, relating to poor gene expression. Applicants respectfully traverse.

To be enabling, the disclosure must contain sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. MPEP 2164.01 (August 2001). The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. Id. (quoting *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). However, the fact that experimentation may be extensive, or complex, does not necessarily make it undue, if the art typically engages in such experimentation. MPEP §2164.01 (August 2001) citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983) aff'd. sub nom., *MIT v.*

A.B. Fortia, 774 F.2d 1104 (Fed. Cir. 1985) and §2164.06 (August 2001) citing *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.. 1988).

As an initial matter, applicants respectfully submit that the Examiner's assertion that transfection of mRNA results in poorer gene expression than DNA is, for enablement purposes, irrelevant. The instant claims recite methods of inhibiting tumor growth in a subject bearing a tumor, wherein a nucleic acid encoding at least one anti-angiogenic protein or peptide is administered in a carrier. The relevant inquiry, therefore, is whether one skilled in the art would be able to practice the claimed methods of delivering RNA.

Methods for successful delivery of mRNA to cells were known in the art by the time the present application was filed. Accordingly, one skilled in the art would recognize that RNA may successfully be used in the claimed methods. Thus, Malone et al. described successful RNA transfections into cells in 1989, and U.S. Patent No.5,589,466 ("Felgner") describes successful RNA delivery *in vivo*. Moreover, Felgner states that the transitory nature of mRNA in cells can be a major advantage in gene therapy, as is the fact that the mRNA does not have to penetrate the nucleus to direct protein synthesis. Felgner, column 12, lines 32-40. Moreover, mRNA expression is more rapid, though of a shorter duration, than DNA expression. Id. column 12, lines 62-64. In sum, applicants respectfully submit that the evidence demonstrates that cellular and *in vivo* RNA delivery and expression are fully enabled and request withdrawal of the rejection.

Second, the Examiner asserts that the specification fails to provide guidance regarding RNA transfections, alleging that the applicants must show, for example, the amounts of specific RNAs which would be required to practice the claimed methods, the amount of carriers necessary, or how to increase the stability of RNA for purposes of transfections and expression *in vivo*. Applicants respectfully disagree. Thus, at page 20, lines 16-20, the specification states that the amount of nucleic acid to be administered can be, for example, from 1 to 60 μg. This range is applicable whether the nucleic acid is DNA or RNA.

These exemplified ranges are in accordance with those reported by other workers, such as Felgner, which discloses a range of 0.5 mg/kg to 5 mg/kg for *in vivo* delivery of either DNA or RNA. See column 15, lines 48-51. As stated in the instant specification, the quantity of administered nucleic acid, as well as the amount of carrier, can depend upon the age, weight, and

sex of the subject as well as factors such as the tumor volume and rate of tumor growth within the subject. Determination of appropriate dosages is routine and well within the skill of the routineer. Accordingly, applicants respectfully submit that the instant claims are fully enabled and request withdrawal of the rejection.

Finally, applicants respectfully submit that, rather than directing the rejection to the instant claims, the Examiner's rejection appears to be a wholesale rejection of the field of gene therapy in general. Thus, the Examiner concludes that "one of skill in the art would not have expected that the claimed invention could be operational without some improvement in the state of the art." However, this conclusion is at odds with the number and variety of gene therapy patents issued by the USPTO in recent years.[1] See, for example, U.S. Patent No. 6,135,976, claim 9, which claims a method of performing gene therapy, where the gene therapy agent is an RNA viral vector or plasmid. It is at least inconsistent for the Examiner to reject the present claims due to the alleged inoperability of the entire field of gene therapy while at the same time the PTO has issued literally dozens of patents directed to gene therapy. Moreover, it is improper for the Examiner to impose upon the applicants the burden of "improving" the state of the art. The instant specification fully enables one skilled in the art to practice the invention in accordance with the conventional wisdom in the field. Applicants respectfully submit that nothing further is required, and request withdrawal of the rejection.

Claim Rejections Under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 21-35 as indefinite allegedly because it is unclear whether the term "such carriers" is limited only to liposomes, cationic polymers, and micelles. Without acquiescing in the rejection, applicants have amended claims 21 and 26 to obviate this rejection.

Claims 22 and 28 are also rejected as indefinite for alleged lack of antecedent basis. Without acquiescing in the rejections, these claims have also been amended to obviate the rejections.

[1] A simple search on the USPTO website for patents with the term "gene therapy" in the title, issued between 1996 and 2002, yields 146 issued U.S. patents.

Conclusion

In view of the above remarks and amendments, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

Respectfully submitted,

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PATENT TRADEMARK OFFICE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please amend the claims to read as follows:

21. (Amended) A method for inhibiting tumor growth in a subject bearing a tumor, which comprises administering to the subject RNA encoding at least one anti-angiogenic protein or peptide in a carrier whereby the RNA is expressed and tumor growth is inhibited, wherein the carrier is selected from the group consisting of **[lipsomes]** **liposomes**, cationic polymers, micelles **[or combinations of such carriers]** **and a combination thereof**.

22. (Amended) The method of claim 21, wherein the **[injection is]** **RNA and carrier are administered via** intravenous injection.

26. (Amended) A method for providing anti-angiogenic therapy to a subject in need thereof, which comprises administering by injection to the subject RNA encoding at least one anti-angiogenic protein or peptide in a carrier whereby the RNA is expressed and angiogenic growth is inhibited, wherein the carrier is selected from the group consisting of **[lipsomes]** **liposomes**, cationic polymers, micelles **[or combinations of such carriers]** **and a combination thereof**.

28. (Amended) The method of claim 26, wherein the injection is **[injection]** **made** into **[the]** **a** tumor **in the subject**.